UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/661,804	09/12/2003	Gerold Schuler	106985-8 KGB	8361

27384 7590 08/31/2010

Briscoe, Kurt G.
Norris McLaughlin & Marcus, PA
875 Third Avenue, 8th Floor
New York, NY 10022

EXAMINER	
JUEDES, AMY E	

ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
08/31/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/661,804	SCHULER ET AL.	
	Examiner	Art Unit	
	AMY E. JUEDES	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 June 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12 and 25-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12 and 25-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/16/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment and remarks, filed 6/16/10, are acknowledged.

Claims 12 and 33 have been amended.

Claims 12 and 25-33 are pending and are under examination.

2. In view of Applicant's amendment to the claims, the rejection under 112 second paragraph is withdrawn.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12 and 25-32 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

a method to remove CD4+CD25+ regulatory T cells comprising isolating a population of CD4+CD25+ T cells and testing the isolated CD4+CD25+ T cells for expression of CTLA-4 by contacting the cells with a CTLA-4 antibody,

does not reasonably provide enablement for:

a method to remove CD4+CD25+ regulatory T cells comprising contacting human blood comprising CD4+CD25+ regulatory T cells with antibodies specific for CD4/CTLA-4 or CD25/CTLA-4 and removing said CD4+CD25+ regulatory T cells from the human blood.

As set forth previously, The specification disclosure is insufficient to enable one skilled in the art to practice the invention as claimed without an undue amount of experimentation. Undue experimentation must be considered in light of factors including: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill in the art, the level of predictability of the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention, *in re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

"The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ

18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling (MPEP 2164.03)" The MPEP further states that physiological activity can be considered inherently unpredictable.

The specification provides insufficient guidance to enable claims drawn to the method as broadly claimed. As an initial matter, it is noted that it is not clear how contacting with the CD4/CTLA-4 or CD25/CTLA-4 antibodies relates to the removal of CD4+CD25+ regulatory T cells. Thus, the claims are missing essential steps indicating how the CTLA-4 antibodies relate to the removal of CD4+CD25+ regulatory T cells. It appears that the claims encompass removing the CD4+CD25+ regulatory T cells by separating the cells that are bound to the CD4/CTLA-4 or CD25/CTLA-4 antibodies. However, CTLA-4 is primarily expressed as an intracellular molecule. In fact, CD4+CD25+ regulatory T cells in human blood only express intracellular CTLA-4, and do not express surface CTLA-4 (see Jago et al., 2004). Therefore, contacting human blood cells with a CTLA-4 antibody will not result in binding to CD4+CD25+ regulatory T cells in the absence of a step of permeabilizing the cell membrane, since said regulatory T cells only express CTLA-4 intracellularly. Thus, using a CTLA-4 antibody in a method of isolating functional CD4+CD25+ regulatory T cells, as is encompassed by the instant claims, is highly unpredictable.

Given the unpredictability of the art, the instant specification must provide a sufficient and enabling disclosure, commensurate in scope with the instant claims. The specification discloses specific examples of removing CD4+CD25+ regulatory T cells by purifying CD4+ T cell by negative selection, and contacting said CD4+ T cells with an antibody specific for CD25 to purify (i.e. remove) CD4+CD25+ regulatory T cells. Thus, the only guidance provided by the instant specification regarding the removal of CD4+CD25+ T cells is to select cells expressing CD4 and CD25 markers. The only examples provided relating to the use of CTLA-4 antibodies is to detect expression of CTLA-4 on already purified CD4+CD25+ T cell populations. No examples are provided in which CD4/CTLA-4 or CD25/CTLA4 antibodies are used to remove CD4+CD25+ regulatory T cells, as is encompassed by the instant claims. In fact, the instant specification on pages 11-12 discloses that CD4+CD25+ regulatory T cells in human blood do not express CTLA-4 at the surface. While the instant specification demonstrates that CTLA-4 is expressed intracellularly in regulatory T cells, an antibody can not bind to intracellular CTLA-4 in the absence of a permeabilization step, which is not recited in the instant claims. Furthermore, the instant claims are drawn to removing CD4+CD25+ regulatory T cells, and further testing said T cells in functional assays. Permeabilized T cells would not function in said assays. Thus, given the unpredictability of the art and the lack of guidance provided by the instant specification, it would require undue experimentation to use a CTLA-4 antibody in a method of removing CD4+CD25+ regulatory T cells as broadly claimed.

Applicant's arguments filed 6/16/10 have been fully considered, but they are not persuasive.

Applicant argues that the specification in Example 2 teaches that CD4+CD25+ T cells express a low level of surface CTLA-4, and demonstrates in Fig. 1B that 23% of

CD4+CD25+ T cells were positive for CTLA-4. Applicant notes that the use of antibodies specific for surface markers for cell separation has been know in the art for a long time, the skilled artisan would be able to remove CD4+CD25+ T cells from human blood with antibodies that bind to CTLA-4.

The instant claims are drawn to a method of "removing" CD4+CD25+ T cells from human blood comprising separating cells from the blood that are bound to CD4 and CTLA-4 antibodies or CD25 and CTLA-4 antibodies. However, the specification demonstrates that, at best, CD4+CD25+ T cells express a very low level of CTLA-4. Furthermore, the level of surface CTLA-4 expressed by CD4+CD25+ T cells seems to be quite variable. For example, the frequency of CD4+CD25+ T cells that express CLTA-4 in Fig1C appears to be well below 23%. Furthermore, in the experiments performed by Jago et al, CD4+CD25+ T cells were almost uniformly surface CTLA-4 negative. Thus, by separating cells bound to CD4/CTLA-4 or CD25/CTLA-4 antibodies, as recited in the amended claims, the instant method would result in the removal of, at best, a very small fraction of total CD4+CD25+ T cells (i.e. less than 20% of the cells). Furthermore, depending of the particular subject, the method would remove almost no CD4+CD25+ T cells, since not all blood samples comprise a population of CD4+CD25+ T cells with significant CTLA-4 surface expression (as taught by Jago et a.). The specification on page 10 discloses that the removal process is intended to be performed by immunoabsorption of blood flowing through columns to remove CD4+CD25+ T cells and enhance in vivo immunity (i.e. after re-introduction of the blood from which said T cells have been removed). Thus, based on the teachings of the instant specification, the "removal" process encompassed by the instant claims includes removal of a sufficient level to result in a decreased capacity of regulatory T cells in the resulting blood population. However, it would be highly unpredictable whether a sufficient degree of "removal" to inhibit regulatory T cell capacity in the resulting population could be performed by a process that would result in the removal of only a small fraction of the total CD4+CD25+ T cells. Furthermore, no examples are provided in which CD4/CTLA-4 or CD25/CTLA4 antibodies are used to remove CD4+CD25+ regulatory T cells. While it would be feasible to remove CD4+CD25+ regulatory T cells by

separating cells bound to CD4, CD25, and CTLA-4 antibodies, the instant claims broadly encompass removal using only CD4/CTLA-4 or CD25/CTLA-4 antibodies. The skilled artisan would not be able to practice the full scope of the instant claims by performing the method steps of the instant claims.

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 33 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Koulis et al., February 2001, in view of Read et al., 2000 (both of record) and Leung et al., 1995.

As set forth previously, Koulis et al. teach a method for isolating (i.e. removing) CD4+CD25+ regulatory T cells from human peripheral blood comprising isolating a PBMC population from total blood, and isolating a population of CD4+CD25+ T cells from said PBMC population. Since PBMCs comprise CD4+ T cells, said PBMC population is a population of CD4+ T cells from the blood, as recited in the instant claims. Koulis et al. also teach that the CD4+CD25+ T cells suppress the proliferation of T cells in a co-culture experiment in a cytokine independent manner.

Koulis et al. do not teach testing the CD4+CD25+ T cells for constitutive expression of CTLA-4.

Read et al. teach that intracellular CTLA-4 is constitutively expressed by CD4+CD25+ regulatory T cells in mice, and that it plays a role in their suppressive function. Leung et al. teach antibodies that can be used to measure CTLA-4 expression in human T cells.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to test the human regulatory T cells of Koulis et al., for the expression of CTLA-4, as taught by Read et al. and Lueng et al. The ordinary artisan at the time the invention was made would have been motivated to do so in order to determine if human regulatory T cells constitutively express CTLA-4, as is the case in mouse regulatory T cells. Furthermore, the ordinary artisan would have had a reasonable expectation of success in testing for CTLA-4 expression, since Leung et al. teach antibody reagents that can be used to measure CTLA-4 expression in human T cells.

Applicant's arguments filed 6/16/10 have been fully considered, but they are not persuasive.

Applicant argues that isolation of PBMC does not meet the limitation of isolating CD4+ T cells from the blood, as recited in the instant claims.

Koulis et al. teach isolating PBMC from the blood (i.e. separating PBMC from other cells in the blood, such as red cells). Since PBMC comprise CD4 T cells, said method can be considered a method of "isolating" CD4 T cells from the initial blood population. Regardless, it is noted that Read et al. teach an alternative process for isolating CD4+CD25+ T cells involving first selecting cells that bind to CD4 antibodies, followed by isolating cells from the CD4+ population that bind to CD25, which results in a 98% pure population of CD4+CD25+ T cells. Thus, it would have been obvious to isolate the CD4+CD25+ T cells using the method of Read et al., since selecting from the various known methods for isolation would involve choosing among a finite number of predictable options which could be pursued with a reasonable expectation of success. A person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense (see *KSR International Co. V. Telefex Inc* 82 USPQ2d 1385).

Applicant further argues that the teachings of Read et al. are limited to mice, and the ordinary artisan would not have had a reasonable expectation that human T cells should express CTLA-4.

It is well established that mice are suitable model for studying the human immune system, and are very similar in terms of T cell phenotype and function. Thus, the ordinary artisan would have had a reasonable expectation that human regulatory T

cells would express CTLA-4 in a similar manner to those of mice. Regardless, the instant claim does not require that the CTLA-4 actually be detected by the T cells, but merely requires "testing" for the expression (i.e. determining the presence or absence of CLTA-4). The ordinary artisan would be motivated to perform such testing, and would have a reasonable expectation of success in performing such testing, given the fact that reagents for testing for human CTLA-4 were readily available.

5. No claim is allowed.

6. **THIS ACTION IS MADE FINAL**. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy E. Juedes, whose telephone number is 571-272-4471. The examiner can normally be reached on 8am to 4:30pm, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Amy E. Juedes
Patent Examiner
Technology Center 1600
/Amy E. Juedes/
Primary Examiner, Art Unit 1644